Amendments to the Specification

On page 1, Field of Invention, lines 6 to 13, please replace the paragraph with the following paragraph.

The present invention relates to synthetic peptides derived from the HR1 region of gp41, and particularly trimers formed therefrom, and their use for production of other antiviral agents having activity against HIV (Human Immunodeficiency Virus). More particularly, the present invention comprises a method for producing antivirals that can inhibit ~~transmision~~ transmission of HIV, by using trimers formed from HR1-derived peptides which contain one or more site-specific amino acid substitutions (as compared to the native sequence) such that the peptide self–associates in solution to substantially a trimeric form.

On page 3, lines 8 to 29, please replace the paragraph beginning "Pioneering potent synthetic peptides" with the following paragraph:

Pioneering potent synthetic peptides which inhibit HIV membrane fusion, thereby preventing transmission of the virus to a host cell, have been described previously (see, e.g., U.S. Patent Nos. 6,258,782 and 6,348,568 assigned to the present assignee). However, it is desirable to design and/or develop new synthetic peptides, peptido-mimetics or small molecules (chemicals) as next generation drugs to inhibit HIV membrane fusion. There are several techniques for identifying peptides or small molecules that inhibit HIV fusion. In one method, a compound may be identified as an HIV fusion inhibitor by its ability to inhibit the formation of DP107/DP178 complexes (see, e.g. U.S. Patent No. 6,750,008, assigned to the present assignee). The basic principle of this method is that compounds which can interfere with the binding reaction between peptide DP107 (T-21) and peptide DP178 (T-20) often exhibit potent antiviral activity as fusion inhibitors. An assay using HR1 and HR2 peptides (N36 and C34 peptides) has also been described (see, e.g., U.S. Patent No. 6,150,088). Care must be exercised as to the concentration of the reactants, as HR1 peptides have a tendency to aggregate in the absence of HR2 peptides (Eckert et al., 1999, *Cell* 99:103-115). Additionally, HR1 peptides predominate in solution in tetrameric form by themselves. Thus, in the absence of HR2 peptide, a non-trimeric structure is presented

to compounds being evaluated for activity as fusion inhibitors. More desirable is a trimer comprised of three HR1 peptides, in evaluating compounds and producing drugs with activity as fusion inhibitors, since the x-ray crystallographic structure of the HR1/HR2 complex has indicated that, as part of gp41, the HR1 region forms a trimer to which three HR2 regions bind in forming a six-helix bundle *in vivo*.

On page 8, line 18 to page 9, line 8, please replace the paragraph beginning "The term "amino acid substitution", is used in relation to" with the following paragraph:

The term "amino acid substitution" is used in relation to the amino acid sequence of a native sequence of the HR1 region of HIV-1 gp41, and is also used in relation to amino acid sequence of a synthetic peptide provided with the present invention. The term "amino acid substitution" is used in relation to the native sequence, hereinafter for the purposes of the specification and claims, to mean one or more amino acids substitution in or to the amino sequence of the native sequence in producing a synthetic peptide that can self-assemble in solution into a trimeric form, and wherein the synthetic peptide can bind the HR2 region or a peptide derived ~~thereform~~ therefrom, as may be determined by the teachings herein and by using methods routine in the art. Likewise, when comparing synthetic peptides provided with the present invention, reference is often made to the amino acid sequence of one synthetic peptide as containing one or more additional amino acid substitutions when compared to the amino acid sequence of another synthetic peptide. Preferably, the amino acid substitution in the sequence of the synthetic peptide provided with the present invention ranges from 1 to 10 amino acids, and more preferably from 1 to 5 amino acids (the higher range being more desirable for longer peptides, e.g., about 40 or more amino acids in length). The amino acid substitution may comprise a "conservative substitution". As known in the art "conservative substitution" is defined by aforementioned function, and includes substitutions of amino acids having substantially the same charge, size, hydrophilicity, and/or aromaticity as the amino acid replaced. Such substitutions are known to those of ordinary skill in the art to include, but are not limited to, glycine-alanine-valine; isoleucine-leucine; tryptophan-tyrosine; aspartic acid-glutamic acid; arginine-lysine; asparagine-glutamine; and serine-threonine. Such substitutions may also comprise

polymorphisms, as illustrated in FIG. 2, at the various amino acid positions along the HR1 region found in laboratory and/or clinical isolates of HIV.

On page 9, lines 9 to 30, please replace the paragraph beginning "A "compound" is a term used" with the following paragraph:

A "compound" is a term used hereinafter, for the purposes of the specification and claims, to mean a molecule which may include, but is not limited to, a small molecule chemical compound, a natural or synthetic peptide, a mimetic (e.g., peptidomimetic or other mimetic), a polypeptide, an aptamer, a polymer, an oligonucleotide, an antibody or fragment thereof, a polysaccharide, a carbohydrate-containing molecule, an enzyme, an agent, a macromolecule, a metabolite, a combination thereof, and the like. In a preferred embodiment, the compound is a therapeutically deliverable substance; and in a more preferred embodiment, the compound is a therapeutically deliverable substance that can inhibit binding between the HR1 and HR2 regions of HIV gp41, and in a further preferred embodiment, the compound is a therapeutically deliverable substance that can inhibit transmission of HIV to a target cell. A "drug" is a compound or composition of matter which, when administered to an individual (such as a human), induces a desired pharmacological (therapeutic, ~~prophylatic~~ prophylactic, or a combination thereof) effect. In a preferred embodiment, a drug comprises a compound and a pharmaceutically acceptable carrier; and in a more preferred embodiment, the drug comprises a compound and a pharmaceutically acceptable carrier, wherein the drug can be administered in an amount effective to inhibit binding between the HR1 and HR2 regions of HIV gp41 (i.e., a desired pharmacological effect); and in a further preferred embodiment, the drug is a compound and a pharmaceutically acceptable carrier, wherein the drug can be administered in an amount effective to inhibit transmission of HIV to a target cell (i.e., a desired pharmacological effect), and more particularly, to inhibit HIV fusion to a target cell.

On page 10, line 12 to page 11, line 9, please replace the paragraph beginning "The term "reactive functionality", when used herein for purposes" with the following

paragraph.

The term "reactive functionality", when used herein for purposes of the specification and claims, means a chemical group or chemical moiety that is capable of forming a covalent bond and/or is protective (e.g., protects peptide derivatives from reacting with themselves). With respect to chemical groups, a reactive functionality is known to those skilled in the art to comprise a group that includes, but is not limited to, maleimide, thiol, carboxy, phosphoryl, acyl, hydroxyl, acetyl, hydrophobic, amido, dansyl, fluorenylmethyoxycarbonyl (Fmoc), t-butyloxycarbonyl (Boc), sulfo, a succinimide, a thiol-reactive, an amino-reactive, a carboxyl-reactive, and the like. A chemical moiety may comprise a linker. Linkers are known to refer to a compound or ~~moeity~~ moiety that acts as a molecular bridge to operably link two different molecules (e.g., a wherein one portion of the linker binds to a peptide provided with the present invention, and wherein another portion of the linker binds to a macromolecular carrier or another antiviral peptide known to inhibit HIV transmission to a target cell). The two different molecules may be linked to the linker in a step-wise manner. There is no particular size or content limitations for the linker so long as it can fulfill its purpose as a molecular bridge. Linkers are known to those skilled in the art to include, but are not limited to, chemical chains, chemical compounds (e.g., reagents), and the like. The linkers may include, but are not limited to, homobifunctional linkers and heterobifunctional linkers. Heterobifunctional linkers, well known to those skilled in the art, contain one end having a first reactive functionality to specifically link a first molecule, and an opposite end having a second reactive functionality to specifically link to a second molecule. It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, Ill.), may be employed as a linker with respect to the present invention. Depending on such factors as the molecules to be linked, and the conditions in which the linking is performed, the linker may vary in length and composition for optimizing such properties as preservation of biological function stability, resistance to certain chemical and/or temperature parameters, and of sufficient stereo-selectivity or size. For example, the linker should not significantly interfere with the ability of the peptide (to which it is linked) to function as an inhibitor of either or both of HIV fusion and HIV

transmission to a target cell. A preferred reactive functionality may be used with the present invention to the exclusion of a reactive functionality other than the preferred reactive functionality.

On page 13, line 21 to page 14, line 13, please replace the paragraph beginning "More particularly, and with reference to FIG. 2" with the following paragraph.

More particularly, and with reference to FIG. 2, in two adjoining heptads (abcdefgabcdefg), the cluster of hydrophobic amino acids comprises the sequence (single letter amino acid code) "IEAQQHLLQLTVWG" (amino acid residues in positions 24 to 37 of SEQ ID NO:1, or polymorphisms thereof, see, e.g., FIG. 2 for some illustrations of HR1 amino acid sequences that differ slightly from SEQ ID NO:1 as a result of viral polymorphisms). A motif of such cluster of hydrophobic amino acids, with the motif referred to hereinafter as the "hydrophobic domain" of the HR1 region, may be generally represented by the sequence "QHLLQLTVW" (amino acid residues in positions 28 to 36 of SEQ ID NO:1 or polymorphisms thereof) and comprising heptad repeat positions "efgabcdef", or represented by the sequence "QHXXZLTVW" comprising heptad repeat positions "efgabcdef", where X is typically leucine or methionine; and Z is typically glutamine, but may also be another amino acid such as lysine or glutamic acid. Thus, for example, a substitution in either the "c" position of the hydrophobic domain (e.g., at amino residue 33 of SEQ ID NO:1 or polymorphisms thereof) or in both the "g" position and the "c" position of this hydrophobic domain of the HR1 region (e.g., at amino acid residue 30 and amino residue 33, respectively, of SEQ ID NO:1 or polymorphisms thereof) alters the ~~oligimerization~~ oligomerization state of the resultant synthetic peptide when in solution. It will be apparent to one skilled in the art that any peptide derived from the native sequence of the HR1 region of HIV gp41 which has antiviral activity (as can be determined using methods standard in the art without undue experimentation), and which contains all or a portion (e.g., no less than "QHLL" or "QHXX" at the carboxy terminus of the native sequence) of the hydrophobic domain, can be used as a native sequence into which one or more amino acid substitutions in the hydrophobic domain may be introduced to produce a synthetic peptide provided with the present invention. For purposes of illustration, such HR1 peptides derived from the native sequence, and

from which a synthetic peptide may be produced, may include, but are not limited to, SEQ ID NOs:1 to 28.

On page 25, lines 13 to 23, please replace the paragraph beginning "In another example" with the following paragraph.

In another example, the synthetic peptide having the amino acid sequence of SEQ ID NO:37 comprises the same amino acid sequence as the synthetic peptide with the amino acid sequence of SEQ ID NO:35 (an amino acid substitution in one or more "a" positions and in one or more ~~"d"positions~~ "d" positions) except for one additional substitution at amino acid residue position 35 of SEQ ID NO:35 (e.g., in a "b" position of a heptad, whereby the arginine is substituted for a lysine). Thus, the synthetic peptide having the amino acid sequence of SEQ ID NO:37 comprises 49 amino acids in length and comprises a heptad repeat of 6 complete heptads and 3 leucine zipper-like motifs. Although synthetic peptides having the respective amino acid sequence of SEQ ID NO:35 and 37 vary by only one residue, as shown in Table 2, the helicity and stability are increased when the arginine residue is substituted for the lysine residue.

On page 32, lines 8 to 21 last paragraph, please replace the paragraph beginning "It is an unexpected result that an amino acid substitution" with the following paragraph:

It is an unexpected result that an amino acid substitution in the either of the C-terminal "e" position and/or in the C-terminal "f" position of the hydrophobic domain, confers the oligomeric state of synthetic peptide to that comprising predominately a trimer in solution (as can be concluded from the data presented in Table 6). More particularly, amino acid substitutions in amino acid residues neighboring (i.e., at the "g" position in the same or adjacent heptad) the C-terminal "e" and "f" positions of the hydrophobic domain failed to switch the oligomeric state to self-assembly into trimers (see, e.g., peptides having the amino acid sequences of SEQ ID NOs: 44-46; and each of which self-assembles into tetramers in solution). Also as shown in Table 6, an amino acid substitution in the either of the C-terminal "e" position and/or in the C-terminal "f" position of the hydrophobic domain can result in a significant increase in helicity for the synthetic peptide, as well as an increase in antiviral activity (e.g., increase in potency; at

least a 3 fold increase in potency) as compared to an HR1 peptide of the native sequence (without ~~substutions~~ substitutions).